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(54) Title: ANTIOXIDANT COMPOSITION COMPRISING ACETYL L–CARNITINE AND α–LIPOIC ACID

(57) Abstract

A composition is disclosed which comprises as characterizing active ingredients acetyl L–carnitine and α–lipoic acid, for the prevention and/or therapeutic treatment of various alterations and pathological states induced by free radicals, that may take the form of a dietary supplement, dietetic support or of an actual medicine.

Antioxidant composition comprising acetyl L-carnitine and α-lipoic acid

The present invention relates to a composition for the prevention and/or treatment of tissular diseases brought about by the presence of free radicals due to environmental pollution; brain or myocardial damages induced by free radicals following cerebral or myocardial ischaemia and attendant riperfusion; of the toxic or diabetic neuropathies and of metabolic disorders in the glucose utilization.

Accordingly, the composition may take the form and exert the action of a dietary supplement or of an actual medicine, depending upon the support or preventive action, or the strictly therapeutic action, which the composition is intended to exert in relation to the particular individuals it is to be used in.

More particularly the present invention relates to an orally, parenterally, rectally or transdermally administrable composition which comprises in combination:

(a) acetyl L-carnitine or a pharmacologically acceptable salt thereof, optionally in combination with at least another "carnitine" where for "carnitine" is intended L-carnitine or an alkanoyl L-carnitine selected from the group comprising propionyl-L-carnitine, valeryl L-carnitine, isovaleryl L-carnitine or their pharmacologically acceptable salts; and

(b) α-lipoic acid.

A systemic deficiency of alkanoyl L-carnitines (ubiquitous naturally-occurring compounds, the greatest concentrations of which are to be found above all in skeletal muscle and in the myocardium) is known to lead to muscular and functional deficits which can be restored to normal by the exogenous administration of these compounds.

The presence of acetyl L-carnitine has been ascertained both at cerebral level and in peripheral nervous tissue where its presence is necessary for normal nerve conduction.

The positive effect of acetyl L-carnitine on mitochondrial activity is also proved by its ability to promote the utilization of the glycolytic pathway for ATP production. These effects are detected particularly at the neuronal level where acetyl L-carnitine has proved capable of preventing neuronal lesions or chronic neuronal degeneration.

In addition to a reduction in the carnitines present in the body during the processes of ageing, a reduction in growth factors (GF-I) is also detected and particularly a reduction in IGF-I (insulin-like growth factor).

IGF-I, IGF-II and relaxin are peptides belonging to the group of proinsulins also called somatomedins.

IGFs exert a homeostatic and trophic action, particularly at both central and peripheral nervous system level, and the clinical use of these peptides has yielded beneficial results in many degenerative nervous disorders including diabetic neuropathy.

The correlations existing between ageing and a reduction in carnitines and growth factors, including IGF-I, and the restoration of the levels of these factors by means of the exogenous administration of acetyl L-carnitine justify the interest in carnitines for the purposes of their use in the prevention and treatment of neurodegenerative diseases, including diabetic neuropathy.

It has been demonstrated that α-lipoic acid also performs an important regulatory function on carbohydrate metabolism and insulin activity. α-lipoic acid is widely distributed in nature in both the vegetable and animal worlds and can be taken with food. Recognised first as a growth factor for a number of micro-organisms, it was then isolated in ox liver as bound to many animal proteins. It acts as an important scavenger of free radicals, above all those deriving from environmental contamination. Recently, it has been shown that this compound is also useful in the regulation of glucose utilization and of insulin activity, so

Since many of the complications associated with diabetes, such as neuropathies and ocular cataracts are mediated by ROS, inhibition of activation of the nuclear transcription factor may constitute a mechanism via which α-lipoic acid may intervene in the prevention of diseases related to diabetes. Furthermore, one should also bear in mind that, in diabetic subjects, the concentrations of α-lipoic acid are lower than normal values and that the administration of α-lipoic acid may restore these levels to normal. It thus has an additive effect to that of insulin in glucose transport to the cell membranes.

Chronic exposure to high concentrations of glucose may lead to a non-enzymatic reaction between glucose and proteins and to the spontaneous formation of highly reactive proteins known as end products of glycosylation (Advanced Glycosylation End Products = AGEs). Among these, the gylcosylation products of glucose and albumin, glucose and collagen, and glucose and haemoglobin are those most studied. The effects that AGEs give rise to in tissues and cells are all relevant factors in explaining a large proportion of diabetic diseases at nervous, muscular and endothelial level.

AGEs, in fact, enhance the synthesis of the components of the extracellular matrix, increase endothelial permeability and the formation of immune complexes and cytokines, and cause neuronal and retinal ischaemia, myelin accumulation and myelinic degeneration. A number of these compounds are formed both in the course of diabetes and during ageing.

A correlation between AGEs and activation of NF-IKB has recently been demonstrated, as has the ability of α-lipoic acid to inhibit this reaction.

Protein glycation and glucose oxidation by glucose at high concentrations together with free radicals may, therefore, be another of the causes responsible for the tissue abnormalities - particularly nerve tissue abnormalities - associated with diabetes. The presence of α-lipoic

carnitine, propionyl L-carnitine, valeryl L-carnitine and isovaleryl L-carnitine or their pharmacologically acceptable salts thereof.

The (a):(b) weight-to-weight ratio ranges from 100:1 to 1:10.

Toxicological tests

Both carnitines and α-lipoic acid are well known for their very limited toxicity and good tolerability. These favourable toxicological characteristics of carnitines and α-lipoic acid have been confirmed by combining these components and administering them at high doses both to rats and mice. In these animals, in fact, it proved possible to administer amounts of up to more than 250 mg/kg of acetyl L-carnitine or 100 mg/kg of α-lipoic acid parenterally, as well as of 250 mg/kg of a mixture of carnitines (acetyl L-carnitine, propionyl L-carntine, isovaleryl L-carnitine combined in a 1:1 weight ratio to one another) and more than 500 mg/kg of acetyl L-carnitine, 500 mg/kg of the carnitine mixture and 200 mg/kg of α-lipoic acid orally without any of the animals thus treated dying.

Also prolonged administration via the diet for 30 consecutive days, both in a group of rats and in a group of mice, of 200 mg/kg of acetyl L-carnitine or 200 mg/kg of the carnitine mixture together with 100 mg/kg of α-lipoic acid proved to be well tolerated and led to the detection of no signs of toxicity. Both the weight gain and the various blood-chemistry tests performed in these animals showed normal values, as did the findings of histopathology tests performed on the main organs after sacrificing the animals at the end of treatment.

Neuroprotective activity tests in experimental cerebral ischaemia

In view of the fact that lesions due to cerebral ischaemia are related to the production of free radicals and of nitrous oxide and that both carnitines and α-lipoic acid afford protection against the toxic action of free radicals, in these tests cerebral ischaemia was induced by

Experimental diabetic hyperglycaemia tests

Hyperglycaemia, whether through the formation of protein glycosylation products (AGEs) or through metabolic hypoxia, is one of the underlying factors responsible for diabetic disease and particularly for diabetic neuropathy.

Controlling serum glucose is therefore one of the most important means of preventing diseases related to diabetes. In these tests, experimental diabetes was induced in rats, and tests were then performed to establish whether the induced hyperglycaemia could be reduced by the administration of acetyl L-carnitine, or carnitine mixture, or α-lipoic acid, or combinations of these products. The hyperglycaemia was induced by subcutaneous injection of alloxan (100 mg/kg) in the rat, and those rats were considered hyperglycaemic which presented serum glucose levels above 450 mg/dl seven days after the alloxan injection.

Treatment with the test substances was given orally for a period of three weeks. At the end of this period, serum glucose was measured in the various groups of rats, both hyperglycaemic and treated.

The results obtained demonstrate that both carnitines and α-lipoic acid alone are capable of only slightly lowering the high initial serum glucose values, but the most significant result is that which appears after administration of carnitines in admixture with α-lipoic acid. In this case, particularly with the combination of acetyl L-carnitine and α-lipoic acid, there is a marked synergistic action of the two products which are capable of bringing serum glucose values down almost to normal.

administered. The sorbitol concentration appeared to be decreased in all animals treated, but the most marked reduction was that detectable in the animals treated with the combination of α-lipoic acid and carnitines, and the lowest values were recorded in the group treated with the combination of acetyl L-carnitine and α-lipoic acid.

The results of these tests also show a surprising degree of synergistic potentiation activity between α-lipoic acid and carnitines.

Table 3

Sorbitol content in ocular lens and sciatic nerve in the diabetic rat

Treatment	Sorbitol (nmol/mg) Lens	Sciatic nerve
Controls	0.44 ± 0.06	0.078 ± 0.008
Diabetics	40.2 ± 3.9	1.85 ± 0.21
Acetyl L-carnitine	32.7 ± 2.5	1.15 ± 0.11
Carnitine mixture	30.5 ± 2.9	1.05 ± 0.09
α-lipoic acid	30.8 ± 3.2	1.08 ± 0.10
Acetyl L-carnitine + α-lipoic acid	14.7 ± 2.8	0.55 ± 0.08
Carnitine mixture + α-lipoic acid	16.4 ± 1.9	0.65 ± 0.07

Tests of survival and growth of nerve cells treated with IGF-I, carnitines and α-lipoic acid

In view of the important role that insulin-like growth factor (IGF-I) plays in protecting the functional integrity of nerve cells, particularly against toxic lesions such as those presenting in the course of diabetic diseases, we considered whether the activity of IGF-I favouring the growth and survival of brain cells was facilitated by the presence in the culture medium of carnitines, or α-lipoic acid, or of these products in combination. To this end, brain cells of Wistar rats were isolated according to the method described by Thanguipon (Thanguipon W., Dev. Brain Res., 11, 177, 1983) and were distributed on plates with a density of 3 x $10^5/cm^2$. To the culture medium was added cytosine arabino-furanoside (10 mM) to prevent the replication of non-neuronal

Sciatic nerve regeneration tests in diabetic rats

Rats with induced diabetes whose sciatic nerve has been cut present inferior regenerative activity to that of normal rats.

These tests were conducted to investigate whether regeneration of the sciatic nerve in diabetic rats may be accelerated by treatment with acetyl L-carnitine, carnitine mixture, or α-lipoic acid, or combinations of these products. The technique used in these tests is the one described by Fernandez (Fernandez E., Int. J. Clin. Pharmacol. Res., 10, 85, 1990).

Diabetes (serum glucose above 450 mg/dl) was induced in a group of rats by subcutaneous injection of 100 mg/kg of alloxan. Acetyl L-carnitine, carnitine mixture and α-lipoic acid were administered with the diet in such a way that the daily intake was 200 mg/kg of acetyl L-carnitine, 200 mg/kg of carnitine mixture (acetyl L-carnitine + propionyl L-carnitine + isovaleryl L-carnitine in a 1:1 weight ratio to one another) and 50 mg/kg of α-lipoic acid. The compounds were administered a week before cutting the sciatic nerve and for thirty days after cutting.

The sciatic nerve was cut under anaesthesia and after exposing 1 cm of it at the level of the sciatic foramen. The border of the lesion was marked with an epineural suture. Thirty days after cutting the nerve, the tissue of the tibial nerve, one of the main divisions of the sciatic nerve, was examined, after sacrificing the animals. Four cross-sections of the tibial nerve measuring approximately 4 mm in length were thus subjected to morphological and morphometric examination by means of a semiautomatic image analyser (Zeiss Videoplan Image Analyser).

The number of regenerating axons and their density per 100 nm^2 were counted, as well as the degenerate elements. It thus proved possible to detect the diabetes-induced degeneration of the tibial nerve elements,

from the gastrocnemius and its distal tendon cut and connected up to an isometric transducer which recorded the muscular contraction force (MCF). The muscle was stimulated via the sciatic nerve by means of two electrodes inserted at a distance of 10 mm from the nerve and connected up to a stimulator.

A bipolar electrode was placed in the distal end of the muscle for displaying the electromyogram via an oscilloscope.

The NMCV was measured in m/sec, dividing the distance between the stimulation electrodes by the mean difference in latency between the start of the ECG potentials evoked in the two sites. The MCF was expressed in mm.

Table 6

Neuromuscular conduction tests in the diabetic rat (after 4 weeks)

Treatment	NMCV (m/sec)	MCF (mm)
Controls	42.2 ± 2.4	49.3 ± 3.1
Diabetics	34.5 ± 2.1	34.6 ± 2.9
Diabetics + acetyl L-carnitine	38.5 ± 1.9	40.6 ± 3.4
Diabetics + carnitine mixture	39.9 ± 2.1	41.2 ± 2.7
Diabetics + α-lipoic acid	40.1 ± 1.5	41.9 ± 3.3
Diabetics + acetyl L-carnitine + α-lipoic acid	43.4 ± 2.4	48.9 ± 3.9
Diabetics + carnitine mixture + α-lipoic acid	42.0 ± 3.1	47.5 ± 4.1

Motor co-ordination abnormality test

These tests were conducted in "wobbler mice", that is to say animals that present an unsteady, staggering gait, an abnormal position of the paws and a reduced speed of movement. These abnormalities are related to progressive atrophy of the motoneurons and musculo-cutaneous nerve fibres, particularly as affecting the anterior limbs. The tests were conducted according to the procedure proposed by Mitsumoto (Mitsumoto H., Annal. Neurol., 36, 14, 1994). After diagnosis, the wobbler mice were treated orally for twenty days

Tests of cisplatin-induced sensory neuronal lesions

The prolonged administration of cisplatin to experimental animals is capable of causing lesions at the level of the sensory neurons and of causing marked abnormalities of propioceptive perception.

In these tests, we evaluated the protective effect exerted by the administration, for seven consecutive days, of 300 mg/kg of acetyl L-carnitine orally, or 300 mg/kg of carnitine mixture (acetyl L-carnitine + propionyl L-carnitine + isovaleryl L-carnitine in a 1:1 weight ratio to one another), or of 50 mg/kg of α-lipoic acid, or of these products in various combinations on the toxicity induced by the subcutaneous injection of 10 mg/kg of cisplatin for seven days consecutively.

The proprioceptive sensory perception abnormalities induced by cisplatin in the mouse were evaluated by means of the rotarod test (Apfel, S.C., Ann. Neurol., 29, 89, 1991).

The results obtained in these tests demonstrate that, whereas cisplatin causes a substantial reduction in equilibrium time in cisplatin-treated animals as compared to control animals and reductions of the same order in the animals treated with acetyl L-carnitine or α-lipoic acid alone, the group of animals treated with the combination of acetyl L-carnitine and α-lipoic acid, on the other hand, show an equilibrium capability practically identical to that of the animals not subjected to cisplatin intoxication. In these tests, too, there is a marked, synergistic effect of carnitines and α-lipoic acid.

Illustrative, non-limiting examples of formulations according to the invention are reported hereinbelow.

1)	Acetyl L-carnitine	mg	500
	α-lipoic acid	mg	50
2)	Carnitine mixture (acetyl L-carnitine, propionyl L-carnitine, isovaleryl L-carnitine in identical weight amounts)	mg	500
	α-lipoic acid	mg	50
3)	Acetyl L-carnitine	mg	250
	α-lipoic acid	mg	25
4)	Carnitine mixture (acetyl L-carnitine, propionyl L-carnitine, isovaleryl L-carnitine in identical weight amounts)	mg	250
	α-lipoic acid	mg	25
5)	Acetyl L-carnitine	mg	1
	α-lipoic acid	mg	100
6)	Acetyl L-carnitine	mg	250
	α-lipoic acid	mg	25
	Selenium methionine	μg	50
	Zinc glycinate	mg	10
	Magnesium stereate	mg	20
	Taurine	mg	50
	Vit. E	mg	10
	CoQ_{10}	mg	10
	β-carotene	mg	10
	Vit. C	mg	30

What is meant by pharmacologically acceptable salt of L-carnitine or alkanoyl L-carnitine is any salt of these active ingredients with an acid that does not give rise to unwanted toxic or side effects. These acids are well known to pharmacy experts.

Claims

1. A composition which in combination comprises:

(a) acetyl L-carnitine or a pharmacologically acceptable salt thereof; and

(b) α-lipoic acid.

2. The composition of claim 1, wherein the ingredient (a) further comprises a "carnitine" selected from the group comprising L-carnitine, propionyl L-carnitine, valeryl L-carnitine, isovaleryl L-carnitine or their pharmacologically acceptable salts or mixtures thereof.

3. The composition of claim 1 or 2 wherein the weight ratio (a):(b) is from 100:1 to 1:10.

4. The composition of any of the preceding claims wherein the pharmacologically acceptable salt of L-carnitine or alkanoyl L-carnitine is selected from the group comprising: chloride; bromide; iodide; aspartate, acid aspartate; citrate, acid citrate; tartrate; phosphate, acid phosphate; fumarate, acid fumarate; glycerophosphate; glucose phosphate; lactate; maleate, acid maleate; orotate; acid oxalate; sulphate, acid sulphate; trichloroacetate; trifluoroacetate and methane sulphonate.

5. The composition of any of the preceding claims, which further comprises vitamins, coenzymes, mineral substances and antioxidants.

6. The composition of any of the preceding claims, orally administrable, in the form of a dietary supplement.

7. The composition of any of the preceding claims, orally, parenterally, rectally or transdermally administrable in the form of a medicament.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A23L1/30 A23L1/302 A61K31/385 //(A61K31/385,31:205)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A23L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 98 41113 A (SIGMA TAU IND FARMACEUTI) 24 September 1998 (1998-09-24) abstract page 4, line 1 -page 6, line 16 claims ---	1-13
X	WO 98 33494 A (KOSBAB JOHN V) 6 August 1998 (1998-08-06) page 2, line 9 -page 4, line 22 page 6, line 21 - line 28 page 18, line 27 - line 30 page 24, line 31 - line 37 page 32, line 12 - line 19 page 34, line 11 - line 19 --- -/--	1-13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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